REMARKS

Claims 1-4, 6-23, 25-34, 42, 61, and 71-109 were pending in the subject application. By this Amendment applicants have canceled claims 4, 23, 26, 85, 102 and 105 without prejudice, amended claims 3, 21, 22, 25, 28, 61, 84, 101, 104 and 107-109, and added new claims 110-115. Accordingly, claims 1-3, 6-22, 25, 27-34, 42, 61, 71-84, 86-101, 103, 104 and 106-115 are pending and under examination.

Support for new claims 110-115 can be found in the specification, *inter alia*, on page 13, lines 23-33 and Figures 5 and 12 of the subject specification.

Rejections under 35 U.S.C. §112, first and second paragraphs

On page 2 of the December 26, 2002 Office Action the Examiner rejected claims 4, 23, 85 and 102 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleged that applicants' specification does not disclose the "N" value in the formula S-Pro-Cn.

On page 3 of the December 26, 2002 Office Action the Examiner rejected claims 4, 23, 71, 85 and 102 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that claims 4, 23, 85 and 102 are rendered vague and indefinite because the applicants allegedly did not disclose the meaning of the formula S-Pro-Cn, specifically what is meant by "Pro", and "n".

The Examiner also stated that claim 71 is rendered indefinite

because the claim depends upon canceled claim 69.

In response, applicants have canceled claims 4, 23, 85 and 102 without prejudice. However, for the record, applicants point out that "Pro" and "n" is defined in the specification, *inter alia*, on page 13, lines 23-32, Figure 5 and its corresponding description, and Figure 12 and its corresponding description. Specifically, "Pro" designates a prolinol moiety, and "n" is an integer from 1 to 6 defining the number of C atoms in the chain "C" attached to the prolinol moiety. However, applicants are instead using the formula of claims 86, 103, 110 and 111 to define some of the agents applicants are claiming.

Rejection under 35 U.S.C. § 103(a)

On pages 3-5 of the December 26, 2002 Office Action the Examiner rejected claims 1-3, 6-22, 25-34, 61, 72-101 and 103-109 under 35 U.S.C. 103(a) as allegedly unpatentable over McCormick et al. (U.S. Patent No. 3,067,099), and Stack et al. (U.S. Patent No. 6,037,447, in view of Fraser et al. (U.S. Patent No. 6,180,604).

The Examiner alleged that McCormick et al. teach vancomycin as a well-known antibiotic to treat infection caused by various gram-positive bacteria, referring to table 1 of column 10 of McCormick et al. The Examiner also alleged that Stack et al. teaches glycopeptide compounds that are homologs of vancomycin are effective against gram-positive bacteria and control resistant bacterial strains, such as vancomycin-resistance-enterococci (VRE), and that various bacterial strains that are inhibited or destroyed by the homologs, referring to Table 5. The Examiner then alleged that clearly the two references teach that vancomycin and homologs of vancomycin are effective against gram-positive bacterial.

The Examiner acknowledged that the instant invention differs from the cited references in that the cited references do not teach the addition of a second agent effective against vancomycin resistant bacteria. However, the Examiner alleged that the secondary reference, Fraser et al., teaches compounds derived from the applicants' compounds of claims 86 and 103. The Examiner alleged that the compound is indolicidin which can be combined with glycopeptides, such as vancomycin, to inhibit cell wall synthesis, prevent peptidoglycan elongation, thus re-sensitizing vancomycin. The Examiner also alleged that Fraser et al. teaches that the indolicidin compounds are effective against various gram-positive bacteria as disclosed in Table 5 in column 31 of Fraser et al. The Examiner concluded by alleging that applicants are merely combining known antibiotics and antibacterial agents into a single composition to increase its combined and additive antibacterial effects in the absence of evidence to the contrary.

In response, applicants respectfully traverse the Examiner's position on the ground that none of the cited references teaches that infection by vancomycin resistant Gram-positive bacteria can be treated by vancomycin and an agent which cleaves an ester bond in the cell wall peptide precursors of the bacteria, nor do any of the references teach or suggest any of applicants' specific agents. None of the references teach or suggest an agent which cleaves an ester bond in the cell wall peptide precursors of the resistant bacteria.

McCormick et al. relates generally to vancomycin, without addressing how to deal with vancomycin resistant bacteria. Stack et al. relates to glycopeptide dimers of vancomycin and dimers of vancomycin derivatives, which are asserted to be useful for the control of vancomycin resistant enterococci. Neither

McCormick et al. nor Stack et al. even mention using an agent which cleaves an ester bond in the cell wall peptide precursors of the vancomycin resistant bacteria to control the bacteria.

Fraser et al. fail to remedy the deficiencies of McCormick et al. and Stack et al. Initially, applicants respectfully point out that, contrary to the Examiner's assertion, Fraser et al. do not disclose compounds which are "derived from applicants' compounds of claims 86 and 103." Fraser et al. fail to disclose any compound resembling the compounds of applicants' claims 86 and 103. Fraser et al. disclose indolicidin peptide analogs for treating bacterial infections. Indolicidin is a cationic peptide isolated from neutrophils. While indolicidin is effective in controlling Gram-positive and Gram-negative bacteria, indolicidin is toxic to mammals when ingested. See, column 1, line 58 to column 2, line 3 of Fraser et al. The peptide analogs of indolicidin proposed by Fraser et al. are asserted to have certain advantages over indolicidin, including being less toxic to mammals. However, neither indolicidin nor the peptide analogs of Fraser et al. are disclosed to cleave an ester bond in the cell wall peptide precursors of the vancomycin resistant bacteria to control the bacteria.

Applicants note the Examiner's assertion that indolicidin "can be combined with glycopeptides, such as vancomycin, to inhibit cell well [sic] synthesis, prevent peptidoglycan elongation, thus re-sensitizing vancomycin." While it may be that indolicidin can be combined with glycopeptides, such as vancomycin, it is not disclosed in Fraser et al. whether such a combination would inhibit cell wall synthesis, or prevent peptidoglycan elongation, or result in re-sensitizing the bacteria to vancomycin. Applicants find no support for this assertion in Fraser et al. If the Examiner continues to rely on this assertion, applicants

respectfully request clarification of the basis for this assertion. However, applicants also point out that, even if supported, this assertion by itself fails to make obvious applicants' claims which recite that the agent *cleaves* an ester bond.

Applicants have from their research developed a molecular model of the key elements necessary for the selective and catalytic cleavage of the ester bond in the cell wall peptide precursors which make bacteria resistant to antibiotics. The key elements are discussed, *inter alia*, on pages 20 to 36 of the subject application. As noted on page 36, lines 4-20, applicants' disclosed molecular model allows for the design of molecules that disable the antibiotic-resistance mechanism of bacteria, thus re-sensitizing the bacteria to antibiotics, such as vancomycin. Molecules designed according to applicants' model can then be used in conjunction with available antibiotics.

Furthermore, applicants' dependent claims 3, 22, 84 and 101 have been amended to specify that the agent which cleaves the ester bond in the cell wall peptide precursors is not a peptide. Dependent claims 86, 103, 110 and 111 recite an agent which is a small molecule and clearly not a peptide. Accordingly, applicants' dependent claims recite subject matter that is yet further distinguished over the cited references, and should be independently examined.

In conclusion, Fraser et al. alone or in combination with McCormick et al. and Stack et al. do not teach or suggest disabling the antibiotic-resistance mechanism of bacteria by cleaving an ester bond in the cell wall peptides precursors which make the bacteria resistant, as claimed by applicants. Accordingly, applicants respectfully submit that their pending

claims define patentable subject matter and the rejection under 35 U.S.C. § 103 should be reconsidered and withdrawn.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $465.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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Gary J. Gershik 6/13/03
John P. White Date
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Gary J. Gershik
Reg. No. 39,992

CLAIM SET WITH REVISION SHOWN

1. A method of treating a subject afflicted with an infection caused by vancomycin resistant Gram-positive bacteria in which, resistance results from the conversion of an amide bond to an ester bond in the cell wall peptide precursors of the bacteria which comprises administering to the subject an antibacterial amount of vancomycin or a homolog of vancomycin and an amount of an agent effective to selectively cleave said ester bond so as to thereby treat the subject.

2. The method of claim 1, wherein the subject is a human being.

3. (Amended) The method of claim 1, wherein the agent is an activated nucleophile, is not a peptide, and is further characterized by the presence within the agent of an electrophile and chirality complementary to a bacterial cell wall ~~depsi~~peptide.

~~4. The method of claim 1, wherein the agent is represented by the formula S-Pro-C_n.~~

6. The method of claim 1, where the agent catalytically cleaves said ester bond.

7. The method of claim 1, wherein said ester bond is present in the structure D-Ala-D-Lac.

8. The method of claim 1, wherein the agent is administered prior to administering vancomycin or the homolog of vancomycin.

9. The method of claim 8, wherein the agent is administered a sufficient period of time prior to administering vancomycin or the homolog of vancomycin to permit cleavage of said ester bond to be effected.

10. The method of claim 1, wherein the agent and vancomycin or the homolog of vancomycin are administered simultaneously.

11. The method of claim 10, wherein the agent is covalently attached to vancomycin or the homolog of vancomycin.

12. The method of claim 1, wherein the bacteria are Van A, Van B, Van D or Van G Gram positive bacteria.

13. The method of claim 1, wherein the bacteria are Staphylococcus bacteria.

14. The method of claim 12, wherein the bacteria are S. aureus bacteria.

15. The method of claim 1, wherein the bacteria are Enterococcus bacteria.

16. The method of claim 1, wherein the bacteria are Streptococcus bacteria.

17. The method of claim 1, wherein the bacteria are Leuconostoc bacteria.

18. The method of claim 1, wherein the bacteria are Pediococcus bacteria.

19. The method of claim 1, wherein the bacteria are Lactobacillus bacteria.

20. The method of claim 1, wherein the bacteria are Erysipelothrix bacteria.

21. (Amended) A method of killing vancomycin resistant Van A, Van B, Van D, or Van G Gram-positive bacteria which comprises contacting the bacteria with an agent that selectively cleaves D-Ala-D-Lac cell wall depsipeptides in the bacteria in an amount effective to cleave such depsipeptides and an antibacterial amount of vancomycin or a homolog of vancomycin so as to thereby kill the bacteria.

22. (Amended) The method of claim 21, wherein the agent is an activated nucleophile, is not a peptide, and is further characterized by the presence within the agent of an electrophile and chirality complementary to a bacterial cell wall depsipeptide.

~~23. The method of claim 21, wherein the agent is represented by the formula S-Pro-Cn.~~

25. (Amended) The method of claim 21, where the agent catalytically cleaves said ~~ester bond~~ D-Ala-D-Lac cell wall depsipeptide.

~~26. The method of claim 21, wherein said ester bond is present in the structure D-Ala-D-Lac.~~

27. The method of claim 21, wherein the agent is administered prior to administering vancomycin or the homolog of vancomycin.

28. (Amended) The method of claim 27, wherein the agent is administered a sufficient period of time prior to administering vancomycin or the homolog of vancomycin to permit cleavage of ~~said ester bond~~ the D-Ala-D-Lac cell wall depsipeptide to be effected.

29. The method of claim 21, wherein the agent and vancomycin or the homolog of vancomycin are administered simultaneously.

30. The method of claim 29, wherein the agent is covalently attached to vancomycin or the homolog of vancomycin.

31. The method of claim 21, wherein the bacteria are Staphylocoecus bacteria.

32. The method of claim 31, wherein the bacteria are S.aureus bacteria.

33. The method of claim 21, wherein the bacteria are Enterococcus bacteria.

34. The method of claim 21, wherein the bacteria are Streptococcus bacteria.

42. A method of treating a subject afflicted with an infection caused by glycopeptide antibiotic resistant Gram-positive

bacteria in which resistance results from the conversion of an amide bond to an ester bond in the cell wall peptide precursors of the bacteria which comprises administering to the subject an antibacterial amount of a glycopeptide antibiotic and an amount of an agent effective to selectively cleave said ester bond so as to thereby treat the subject.

61. (Amended) A method of killing glycopeptide antibiotic resistant Gram-positive bacteria which comprises contacting the bacteria with an agent that selectively cleaves D-Ala-D-Lac cell wall depsipeptide~~s~~ in the bacteria in an amount effective to cleave such depsipeptide~~s~~ and an antibacterial amount of the glycopeptide antibiotic so as to thereby kill the bacteria.

71. (Amended) The method of claim ~~69~~ 109, wherein the bacteria are Staphylococcus bacteria.

72. The method of claim 61, wherein the bacteria are S. aureus bacteria.

73. The method of claim 71, wherein the bacteria are Enterococcus bacteria.

74. The method of claim 61, wherein the bacteria are Streptococcus bacteria.

75. The method of claim 61, wherein the bacteria are Leuconostoc bacteria.

76. The method of claim 61, wherein the bacteria are Pediococcus bacteria.

77. The method of claim 61, wherein the bacteria are Lactobacillus bacteria.

78. The method of claim 61, wherein the bacteria are Erysipelothrix bacteria.

79. The method of claim 21, wherein the bacteria are Leuconostoc bacteria.

80. The method of claim 21, wherein the bacteria are Pediococcus bacteria.

81. The method of claim 21, wherein the bacteria are Lactobacillus bacteria.

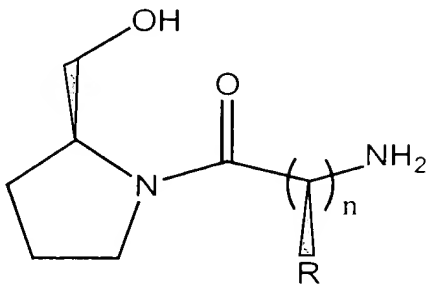
82. The method of claim 21, wherein the bacteria are Erysipelothrix bacteria.

83. The method of claim 42, wherein the subject is a human being.

84. (Amended) The method of claim 42, wherein the agent is an activated nucleophile, is not a peptide, and is further characterized by the presence within the agent of an electrophile and chirality complementary to a bacterial cell wall ~~depsi~~peptide.

~~85. The method of claim 42, wherein the agent is represented by the formula S-Pro-Cn.~~

86. The method of claim 42, wherein the agent has the structure:



wherein n is an integer from 1 to 6 inclusive and R is hydrogen or a C_1 to C_6 straight chain or branched alkyl group.

87. The method of claim 42, where the agent catalytically cleaves said ester bond.

88. The method of claim 42, wherein said ester bond is present in the structure D-Ala-D-Lac.

89. The method of claim 42, wherein the agent is administered prior to administering the glycopeptide antibiotic.

90. The method of claim 89, wherein the agent is administered a sufficient period of time prior to administering the glycopeptide antibiotic to permit cleavage of said ester bond to be effected.

91. The method of claim 42, wherein the agent and the glycopeptide antibiotic are administered simultaneously.

92. The method of claim 91, wherein the agent is covalently attached to the glycopeptide antibiotic.

93. The method of claim 42, wherein the bacteria are

Staphylococcus bacteria.

94. The method of claim 93, wherein the bacteria are S. aureus bacteria.

95. The method of claim 42, wherein the bacteria are Enterococcus bacteria.

96. The method of claim 42, wherein the bacteria are Streptococcus bacteria.

97. The method of claim 42, wherein the bacteria are Leuconostoc bacteria.

98. The method of claim 42, wherein the bacteria are Pediococcus bacteria.

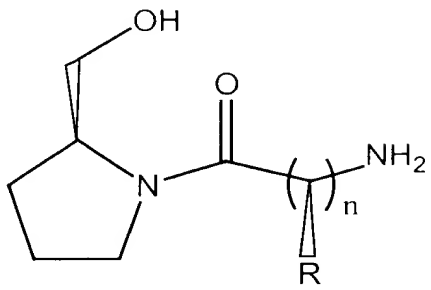
99. The method of claim 42, wherein the bacteria are Lactobacillus bacteria.

100. The method of claim 42, wherein the bacteria are Erysipelothrix bacteria.

101. (Amended) The method of claim 61, wherein the agent is an activated nucleophile, is not a peptide, and is further characterized by the presence within the agent of an electrophile and chirality complementary to a bacterial cell wall depsipeptide.

~~102. The method of claim 61, wherein the agent is represented by the formula S-Pro-Cn.~~

103. The method of claim 61, wherein the agent has the structure:



wherein n is an integer from 1 to 6 inclusive and R is hydrogen or a C_1 to C_6 straight chain or branched alkyl group.

104. (Amended) The method of claim 61, where the agent catalytically cleaves ~~said ester bond~~ the D-Ala-D-Lac cell wall depsipeptide.

~~105. The method of claim 61, wherein said ester bond is present in the structure D-Ala-D-Lac~~.

106. The method of claim 61, wherein the agent is administered prior to administering the glycopeptide antibiotic.

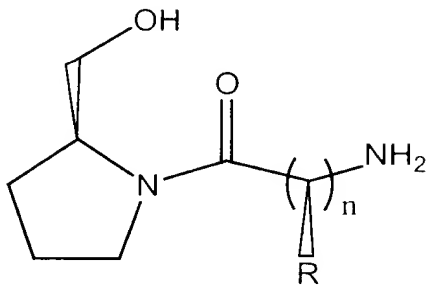
107. (Amended) The method of claim 61, wherein the agent is administered a sufficient period of time prior to administering the glycopeptide antibiotic to permit cleavage of ~~said ester bond~~ the D-Ala-D-Lac depsipeptide to be effected.

108. (Amended) The method of claim ~~106~~ 61, wherein the agent and the glycopeptide antibiotic are administered simultaneously.

109. (Amended) The method of claim ~~61~~ 108, wherein the agent is

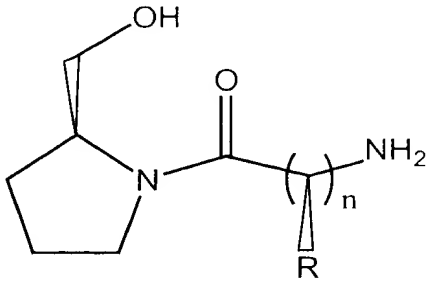
covalently attached to the glycopeptide antibiotic.

110. (New) The method of claim 1, wherein the agent has the structure:



wherein n is an integer from 1 to 6 inclusive and R is hydrogen or a C_1 to C_6 straight chain or branched alkyl group.

111. (New) The method of claim 21, wherein the agent has the structure:



wherein n is an integer from 1 to 6 inclusive and R is hydrogen or a C_1 to C_6 straight chain or branched alkyl group.

112. (New) The method of claim 86, wherein n=5 and R=H.

113. (New) The method of claim 103, wherein n=5 and R=H.

114. (New) The method of claim 110, wherein n=5 and R=H.

115. (New) The method of claim 111, wherein n=5 and R=H.